On June 1, 2009, I presented at Pathology Grand Rounds (combined Beth Israel Deaconess Medical Center-Brigham and Women's Hospital). The title of my talk was "Studies in Human 'Acute Tubular Necrosis'/Acute Kidney Injury: Reaching for Relevance…from Garlic Extract to Hypoxia Inducible Factor". I was introduced by my current Chairman, Dr. Jeffrey Saffitz, who remarked that it was 50 years since I graduated from medical school. Dr. Saffitz, my third Chairman, was appointed in 2006.

My first Chairman, Dr. David Freiman, recruited me in 1967 from Walter Reed Army Institute of Research, where I served in the army for three years. The colonels in charge of the unit were **Kevin Barry** and **Paul Teschan**. Kevin had given me responsibilities inappropriate for a young captain, because I was agreeable, worked very hard, and produced numerous papers. Indeed, I went to the Pentagon, examined curricula vitae, and helped select physicians for the unit, which included luminaries-to-be such as **Drs. Robert Schrier**, **Michael Dunn**, and **Craig Tisher.**

In 1980, 13 years later, Dr. Harold Dvorak became Chairman and, two years thereafter, appointed me Director of Surgical Pathology, a position I continue to hold. Dr. Saffitz appointed Dr. Stuart Schnitt, my former resident, as Director of Anatomic Pathology (Stuart will become head of USCAP in 2010). I continue my position as renal consultant at the Children's Hospital (appointed in 1980 by Dr. Lynne Reed). The patients at this hospital

were very interesting and taught me much about renal growth and development. There was one patient at Children's who really demonstrated, for the first time, the renal destructive capacity of polyoma virus [Rosen S, Harmon W, Krensky A, Edelson PJ, Padgett BL, Grinnell BW, Rubine MS, Walker DL. End stage renal disease apparently induced by polyoma virus (BK type). New Engl J Med 1983; 308:1192-60].

As I look back, everything in my life happened so quickly. My college time was only 2-1/2 years, with just enough credit to be accepted to the University of Illinois Medical School (receiving a Bachelor of Science in Medicine at the end of the second year, which has always looked odd on my CV). After being interested in psychiatry and neurology, my final decision was to become a neuropathologist. I was one of the youngest in my class, graduating when I was 23. I took a rotating clinical internship and was noticed because of my unusual behavior: my intent was to anticipate what the chief resident wanted at morning rounds so that I could reply "That has already been done." This was, indeed, appreciated and the general surgeons and neurosurgeons gave me procedures to do in gratitude. This behavior was common at that time. However, I did not wish to do these things: hernia repair, muscle biopsies, and burr holes, but I did not want to offend them. I delivered 60 babies.

I began my pathology residency in 1960 and Dr. Conrad Pirani's renal biopsy studies intrigued me. This working group included Drs. Pirani, **Victor Pollak**, Robert Muehrcke and **Robert Kark**. Dr. Kark, Professor of Medicine, together with Dr. Muehrcke had effectively introduced the renal biopsy as a practical technique (Kark RM, Muehrcke RC. Biopsy of the kidney in prone position. Lancet, 1954; i: 1047-1049). Dr. Muehrcke was the consummate technician, had served in World War II and supposedly could assemble and disassemble a machine gun in complete darkness. Dr. Kark lent credibility to the group and Dr. Pollak was the driving force – Machiavellian and brilliant. Dr. Pirani's exact position in the hierarchy was never clear to me, but his function was absolutely necessary. I learned later that he never considered me his resident or fellow, but an associate (this surprised me). Indeed, it was not Dr. Pirani but Dr. Pollak that I considered my mentor. Dr. Pollak taught me attention to detail, quantitative analysis, and forced me to learn and apply statistics. This kind of detailed study served me well later in life. In 1963, I married another mentor, my wife, Paula, who introduced me to the outside world, enabling me to interrelate with the complexities of life.

During my time as a resident, I was very productive and presented at the American Association of Pathology and Bacteriology (the organization from which USCAP split one or two years later) an abstract which essentially defined and contrasted lipoid nephrosis and MGN (Rosen S, Pirani CL, Kark RM, Muehrcke RC, Pollak VE. Lipoid nephrosis and idiopathic membranous glomerulonephritis. Am J Pathol 1964; 44:14a). This presentation was met with great skepticism. I did both the morphological and clinical work on the paper which I wrote as well. To my dismay, two years later, Dr.

Pollak submitted the paper essentially as I had written it with his name first, mine second (Pollak VE, Rosen S, Pirani CL, Muehrcke RC, Kark RM. Natural history of lipoid nephrosis and membranous glomerulonephritis. Ann Int Med 1968; 69:1171-97). It was my understanding from Dr. Pirani that he had told Dr. Pollak not to do this. This action of Dr. Pollak's would have consequences. Both Pollak and Pirani were at Michael Reese in Chicago. Dr. Pirani was Chair of Pathology. **Dr. Lou Sherwood**, from Beth Israel Hospital, became Chair of Medicine, a friend whose wife, Judy, I helped with her Ph.D. (Sherwood JB, Robinson SH, Bassan L, Rosen S, Gordon AS. Production of erythrogenin by organ cultures of rat kidney. Blood 1972; 40:189-97). Lou asked me about Pollak. I actually, basically supported him and suggested that he should remain, but Dr. Pirani thought that I said that he should be fired. Pollack, indeed, was dismissed, I think because he was, at times, a difficult and contentious person. For reasons I did not understand, Pirani then had to leave and went to Columbia in New York. He would not speak to me for several years thereafter, but thereafter resumed our previous friendly relationship. At the BI, I collaborated with Phil Steinmetz (winner of the Homer Prize from the American Society of Nephrology) and established the turtle bladder as a model to understand cellular proton secretion (Schwartz JH, Rosen S, Steinmetz PR. Carbonic anhydrase function and the epithelial organization of H+ secretion in the turtle bladder. J Clin Invest 1972; 51:2653-62.). I did the biochemical analysis showing the presence of carbonic anhydrase in the epithelium, a fact which had been denied by Dr. Thomas Maren, who was the leader in the field. Using a histochemical technique for carbonic anhydrase, I established that there was a heterogeneous population of cells. It took sometime for Phil to come to grips with this fact. This work was to lay the groundwork for understanding acidification by the nephron.

In the early 1980's, a new phase of my research began when Dr. Franklin Epstein asked me to work with him and his fellow, **Dr. Mayer Brezis** and later, **Dr. Samuel Heyman**, my present collaborator, examining the morphology of the isolated perfused kidney. Using one micron plastic sections, I was able to accurately quantitate and characterize the severe medullary (mtal) injury which was present in this model. The moment I most remember was when ouabain was added to the perfusate --- sodium transport essentially stopped and minimal injury was seen. This I predicted would be a discovery of great importance. Indeed, Mayer, at a Brigham and Women's Hospital conference, presented this information that showed that mtal injury was dependent on active sodium transport. I begged Dr. Barry Brenner to attend and at the beginning of this conference, he screamed at me that he would be late to pick up his sister-in-law at the airport because of me. After hearing the presentation, he, knowing that we had submitted the manuscript to the JCI, stated to me that this manuscript must be published and he would see to it (Brezis M, Rosen S, Silva P, Epstein F. Selective vulnerability of the medullary thick limb to anoxia in the isolated perfused kidney. J Clin Invest 1984; 73:182-9). Another paper reflecting this concept was published in Science (Brezis M, Rosen S, Silva P, Epstein F. Polyene toxicity in the renal medulla: transport activity mediates injury. Science 1984; 224:66-8). Using this model, we created in vivo models of human acute renal failure, which were totally different

from previous models and more closely mimicked the human situation (Heyman SN, Brezis M, Reubinoff CA, Greenfeld Z, Lechene C, Epstein FH, Rosen S). Acute kidney failure with selective renal medullary injury in the rat (J Clin Invest 1988; 82:401-412; and Agmon Y, Peleq H, Greenfeld Z, Rosen S, Brezis M. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. J Clin Invest 1994; 94:1069-1075). There was a body of studies using the warm ischemia-reflow model which we felt was of little relevance to the human situation of ATN. Most pathologists agreed with us, but many clinical researchers would not recognize this, despite our publications in prominent renal journals (Rosen S, Heyman SN. Difficulties in understanding human "acute tubular necrosis": Limited data and flawed animal models. Kidney Int 2001; 60:1220-1224; and Rosen S, Stillman IE). Acute tubular necrosis is a syndrome of physiologic and pathologic dissociation (J Am Soc Nephrol 2008; 19: 871–875; and S. Heyman, C. Rosenberger and S. Rosen. Experimental ischemia-reperfusion---biases and myths: The proximal vs distal hypoxic tubular injury debate revisited. Kid Int, in press). I was known for my questions and comments, e.g., "Your work has no relevance to human ATN". At an American Society of Nephrology workshop a few years ago, which dealt with this subject, there was agreement that we were correct, but subsequently, the public stance by these researchers was very different. Shortly after 9/11, eight years ago, an international nephrology meeting was held in San Francisco that was not well attended. A nephrologist from Germany, **Christian Rosenberger,** presented a poster on hypoxia-inducible factor which really excited me and this was the beginning of a close collaboration between Berlin, Jerusalem and Boston, which resulted in many papers some of which point to, I believe, possible therapeutic strategies for human ATN/AKI. This collaboration continues and flourishes.

My interests include genitourinary pathology and some aspects of dermatopathology, particularly involving vessel abnormalities. At USCAP, I gave one of the first courses on the renal biopsy and two courses on vasculitis. I was head of the renal night session for five years and asked many young pathologists to participate who would go on to become leaders in the field. I was President of the Renal Pathology Society in 1999, and received the Churg award in 2007. I am exceptionally proud that I received the BIDMC Resident's Teaching Award in 2002 and 2008. I participated in and headed the renal block at Harvard Medical School and was appointed full professor at HMS in 1994.

***The photograph at the beginning is of a painting in my office done by my three grandchildren, Devin, Milan and Sunil (children of my younger son Matthew and his wife Tejas) as a present for my 74th birthday. This comment has been my enthusiastic response when things are really going well. Photographs of my other two grandchildren, Jennifer and Seth (children of my older son Franklin and his wife Karen), given to me at that time, grace my other wall.**

Names in bold print have additional information in a separate file (see file labeled footnotes).